DOI: 10.1002/adsc.200505312

Metal-Free Chemoselective Oxidation of Sulfides to Sulfoxides by Hydrogen Peroxide Catalyzed by *in situ* Generated Dodecyl Hydrogen Sulfate in the Absence of Organic Co-Solvents

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Received: August 6, 2005; Accepted: January 12, 2006

Supporting Information for this article is available on the WWW under http://asc.wiley-vch.de/home/.

Abstract: The mild oxidation of sulfides to sulfoxides with an aqueous solution of H_2O_2 (35%) catalyzed by *in situ* generated dodecyl hydrogen sulfate as Brønsted acid surfactant in the absence of any organic co-solvents and under metal-free conditions is described. The method shows high chemoselectivity and the process is highly green for solid sulfoxides which crystallize out immediately after their formation from the reaction mixture. Liquid sulfoxides can be isolated under high vacuum by bulb-to-bulb distillation or by extraction with Et_2O or EtOAc. Yields of the products are excellent.

Keywords: aqueous hydrogen peroxide; Brønsted acid surfactants; dodecyl hydrogen sulfate; oxidation; sulfides; sulfoxides

Use of aqueous media as a reaction solvent has attracted much attention in synthetic organic chemistry for several reasons.[1] In comparison with organic solvents, water is cheap, safe and reduces the use of harmful organic solvents and leads to the development of environmentally friendly chemical processes.[2] In addition, reactions in aqueous media illustrate unique reactivities and selectivities that are not usually observed in organic media.[3] However, organic solvents are still used instead of water for mainly two reasons; first, most organic substrates are not soluble in water, and as a result, water cannot function as a reaction medium. Second, many reactive substrates, reagents, and catalysts are sensitive towards water and are decomposed or deactivated in aqueous media. A possible new way to improve the solubility of substrates is the use of surface-active compounds that can form micelles[4] or vesicular structures. The use of micellar and vesicle-forming surfactants as catalysts is widespread and has been investigated in detail for different reactions in aqueous solutions.[5,6] Kobayashi and his co-workers have extensively studied the use of transition metal salts as water-tolerant Lewis acids and also Lewis acids surfactants for the promotion of organic reactions in aqueous media.[7] However, from the viewpoints of practicability and applicability, surfactant-aided organic reactions are still at their preliminary stages. Recently, we have successfully applied a micellar aqueous solution of sodium dodecyl sulfate (SDS) for the ring opening of epoxides with various types of nucleophiles[8a] and hetero-Michael additions.[8b]

Organosulfur compounds are versatile intermediates in organic synthesis and are useful for the preparation of biologically and medically important products.[9] In particular, sulfoxides and sulfones have been extensively used for carbon-carbon bond forming reactions,[10] rearrangements,[11] and eliminations.[12] There are many reagents available for oxidation of sulfides to sulfoxides.[13] From the standpoint of green chemistry, nowadays, environmental benign systems for these useful oxidations are desirable. The use of aqueous hydrogen peroxide as a cheap and a clean oxidizer which is transformed into harmless water after performing the oxidation is an excellent alternative to toxic oxidants.[14] For sulfoxidations conducted in the presence of hydrogen peroxide, organic co-solvents such as CH_3CN, CH_3OH, CH_3CH_2OH, CH_3CO_2H, acetone, hexafluoro-2-propanol and phenol should be added to the reaction mixture in order to overcome the insolubility and compatibility of sulfides with aqueous H_2O_2.[15] In this article, we report a green process in which aqueous hydrogen peroxide has been used as an oxidizing agent in the presence of *in situ* generated dodecyl hydrogen sulfate, a Brønsted acid surfactant, for the chemoselective oxidation of sulfides to their sulfoxides in the absence of any organic co-solvents and any metal catalysts.

First, we studied the oxidation of 2 mmol of diphenyl sulfide as a model compound with 8 mmol of aqueous H_2O_2 (35%) as the oxidant. The reaction was allowed

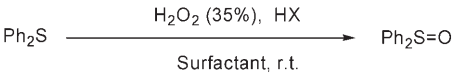
to proceed for 24 h. Analysis of the mixture revealed the formation of the sulfoxide in only 5% yield. Then we decided to run the reaction in acidic media. For this purpose, Brønsted acids with different acidic strengths, such as acetic acid, trichloro- and trifluoroacetic acids, sulfuric and hydrochloric acids were employed. None of the acids were effective and after a long reaction time most of the starting material remained intact. Then, a similar reaction was studied in the presence of 5 mol % of sodium dodecyl sulfate (SDS).The results of this study were also not promising and after 24 h only 20% formation of the corresponding sulfoxide was observed. However, we decided to run the reaction in a mixture of 5 mol % of sodium dodecyl sulfate(SDS) and 10 mol% of the above-mentioned protic acids (Table 1, entries 4–7). Acetic acid as a weak acid in the presence of SDS was not able to conduct this oxidation and the reaction proceeded in only 30% after 24 h (Table 1, entry 3). However, in the presence of strong acids, the rate of the reaction was enhanced and the reaction was completed after 2 h (Table 1, entries 4–6). By consideration of these observations, we may conclude that proton transfer from strong acids to dodecyl sulfate anion is a facile and favoured process which generates dodecyl hydrogen sulfate in the reaction media. However, this *in situ* generated Brønsted acid surfactant shows dual activity. One action is to wrap the sulfide molecule by its non-polar tail and its second function is to bring the H_2O_2 molecule close to the sulfur atom. After this process, the reaction proceeds *via* activation of hydrogen peroxide by hydrogen bonding between $R{-}OSO_3H$ and H_2O_2 in the vicinity of the sulfur atom (Figure 1). Sodium dodecyl sulfate (SDS) also wraps the sulfide molecule but is not able to form the required hydrogen bonding for its activation.

In order to show the general applicability of the protocol, a series of structurally diverse sulfides was converted to their sulfoxides in high yields. All the reactions occurred with absolute chemoselectivity for the sulfoxide formation. In none of the reactions we have presented in this article was the formation of sulfones as over-oxidation products detected in the reaction mixtures. As illustrated in Table 2, various functional groups, including C=C, C=O, −OH and −CN were compatible and the sulfoxides were obtained in almost excellent yields. In several cases, the reaction was complete in less than 10 min (entries 8–11). However, in the cases of diphenyl sulfide and benzyl phenyl sulfide (entries 19 and 20) longer reaction times were required. To further determine the selectivity of the method, the oxidation of diphenyl sulfide in the presence methyl phenyl sulfide was studied. We have observed that the selectivity of the method was excellent and diphenyl sulfide was transformed into its sulfoxide quantitatively without formation of sulfone whereas the formation of a trace amount of methyl phenyl sulfoxide was detected in the reaction mixture (Scheme 1).

The presented protocol follows an environmentally friendly green process in which the solid sulfoxides precipitate out from the aqueous reaction mixture as soon as they are formed. In the case of liquid sulfoxides, bulb-to-bulb distillation under high vacuum resulted in the isolation of the pure sulfoxides. Another alternative is to isolate the liquid sulfoxides by extraction with diethyl ether or ethyl acetate and the evaporation of the solvent.

In conclusion, we have developed a metal-free and organic solvent-less protocol for a highly selective, efficient and *green* process for the chemoselective oxidation of sulfides into their sulfoxides by aqueous solution of H_2O_2 catalyzed by the *in situ* generation of dodecyl hydrogen sulfate. The reactions were highly selective for the conversion of sulfides into their sulfoxides without sulfone formation. Functional groups such as C=C, C=O, OH, or CN tolerate the reaction conditions and remain intact. The operational simplicity, high yields of the

Table 1. Optimization of the oxidation of diphenyl sulfide to its sulfoxide using aqueous solution of H_2O_2.



Entry	Surfactant (5 mol %)	HX (10 equiv. %)	Time [h]	Yield [%]
1	None	None	24	5
2	SDS	None	24	20
3	SDS	CH_3CO_2H	24	30
4	SDS	CCl_3CO_2H	2	95
5	SDS	CF_3CO_2H	2	94
6	SDS	H_2SO_4	2	93
7	SDS	HCl	2	95
8	SDS	HCl	24	80[a]
9	None	HCl	24	10
10	None	CCl_3CO_2H	5	5

[a] 2 mmol H_2O_2 (0.25 mL) was used.

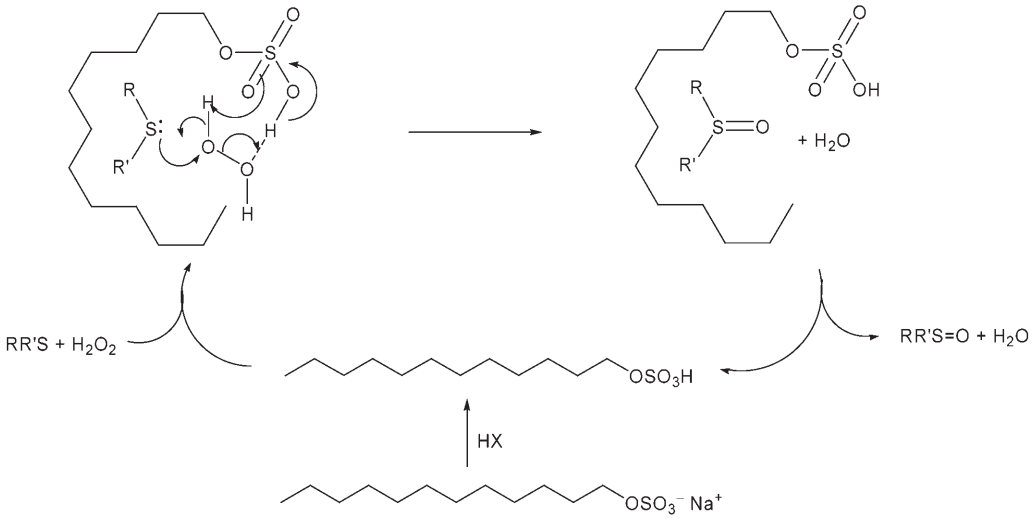
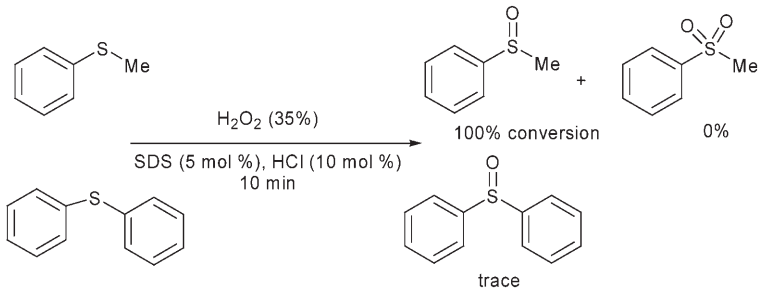


Figure 1. Catalytic role of *in situ* generated dodecyl hydrogen sulfate, a Brønsted acid surfactant, for the activation of hydrogen peroxide by $ROSO_3H$ and solubilization of the lipophilic organic sulfide by its hydrocarbon tail.



Scheme 1.

products, high chemoselectivity, metal-free process and avoiding the use of any organic-solvents while using aqueous media are the advantages of the presented method.

Experimental Section

Sulfoxidation of Methyl Phenyl Sulfide by Aqueous H_2O_2 (35%); Typical Procedure

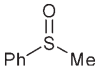
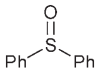
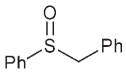
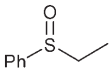
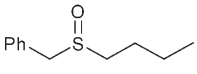
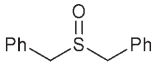
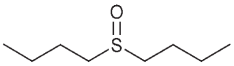
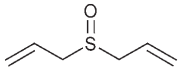
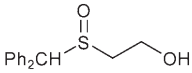
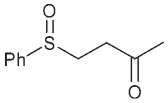
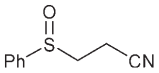
A 10-mL flask was charged with 1 mL (8.0 mmol) of aqueous H_2O_2 (35%), 0.029 g (0.10 mmol) of SDS, and 0.248 g (2 mmol) of methyl phenyl sulfide. To the resulting mixture, 20 μL (0.2 mmol) of aqueous HCl solution were added and stirred at room temperature. The progress of the reaction was followed by TLC. After complete disappearance of the reactant (10 min), the excess amount of H_2O_2 was destroyed by the addition of a saturated aqueous solution of Na_2SO_3 to the reaction mixture. The product was extracted with EtOAc which was separated and dried over anhydrous Na_2SO_4. Evaporation of the solvent under diminished pressure resulted in the almost pure product as a colorless oil; yield: 0.258 g (92%) (see Table 2).

2-(Diphenylmethanesulfinyl)-ethanol (i) [$Ph_2CHS(O)CH_2CH_2OH$]: ^{1}H NMR (250 MHz, $CDCl_3$, TMS): δ = 2.57–2.62 (m, 1H), 2.68–2.75 (m, 1H), 3.83–3.90 (m, 2H), 4.39 (s, 1H, OH), 5.23 (s, 1H), 7.33–7.42 (m, 6H), 7.52–7.59 (m, 4H); ^{13}C NMR (63 MHz, $CDCl_3$,TMS): δ = 52.0, 52.9, 68.9, 126.3, 126.8, 126.9, 1127.4, 1128.0, 134.1, 135.4; MS (EI, 70 eV), *m/e* = 260 [M^+]; anal. calcd. for $C_{15}H_{16}O_2S$: C 69.20, H 6.19; found: C 69.12, H 6.15.

Acknowledgements

The authors are grateful to Iran TWAS Chapter Based at ISMO, Shiraz University Research Council and Ministry of Science, Research and Technology of Iran for the support of this work.

Table 2. Organic solvent-free and metal-less oxidation of sulfides to sulfoxides using an aqueous solution of H_2O_2 catalyzed by *in situ* generated dodecyl hydrogen sulfate, a Brønsted acid surfactant.

Entry	Sulfoxide	Time [min]	Yield[a] [%]
1	**a** 	5	92
2	**b** 	2 h	95
3	**c** 	5 h	91
4	**d** 	10	93
5	**e** 	5	92
6	**f** 	3 h	95
7	**g** 	5	88
8	**h** 	5	85
9	**i** 	10	93
10	**j** 	10	90
11	**k** 	10	92

[a] Yield refers to isolated product; all products were identified by comparison of their IR, NMR, and TLC with those of authentic samples.

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